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Task 3. Analogs of Tetrahydrocannabinol

for

Chemical Corps Procurement Agency

Contract No. DA 18-108-CML-4564
Progress Report
from
October thru November, 1952

[redacted]

SHELL DEVELOPMENT COMPANY
EMERYVILLE CALIFORNIA

Bi-Monthly Report No. 2

on

[redacted]

TASK 3

for

Chemical Corps Procurement Agency

under

Contract No. DA18-108-CML-4564

Period Covered: October through November, 1952

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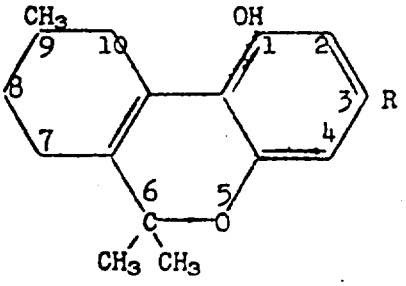
Summary

The preparation of the two most active tetrahydrocannabinol analogs mentioned by Adams[1] is well under way. For one compound ten of the fourteen necessary steps have been completed, and for the other, seven. Concurrently with the above work, various synthetic methods have been tried for the preparation of intermediates which could lead to nitrogen and sulfur analogs of tetrahydrocannabinol.

Introduction

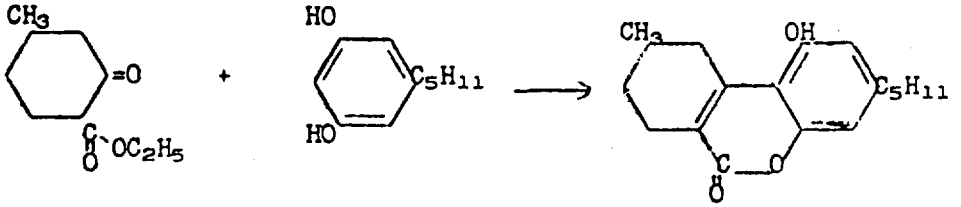
Tetrahydrocannabinol (1-hydroxy-3-n-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran) has the following structure:



R = n-C_5H_{11}

I

To prepare tetrahydrocannabinol, ethyl 5-methylcyclohexanone-2-carboxylate is condensed with 1-n-amyl-3,5-dihydroxy benzene to give 1-hydroxy-3-n-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone.



+ C_2H_5OH + H_2O

This pyrone is then treated with a large excess of CH_3MgI to convert it to the tetrahydrocannabinol.

Tetrahydrocannabinol is the active ingredient of marihuana, and Adams and co-workers at Illinois have effected various changes in the molecule in an effort to produce a more active compound. Changes

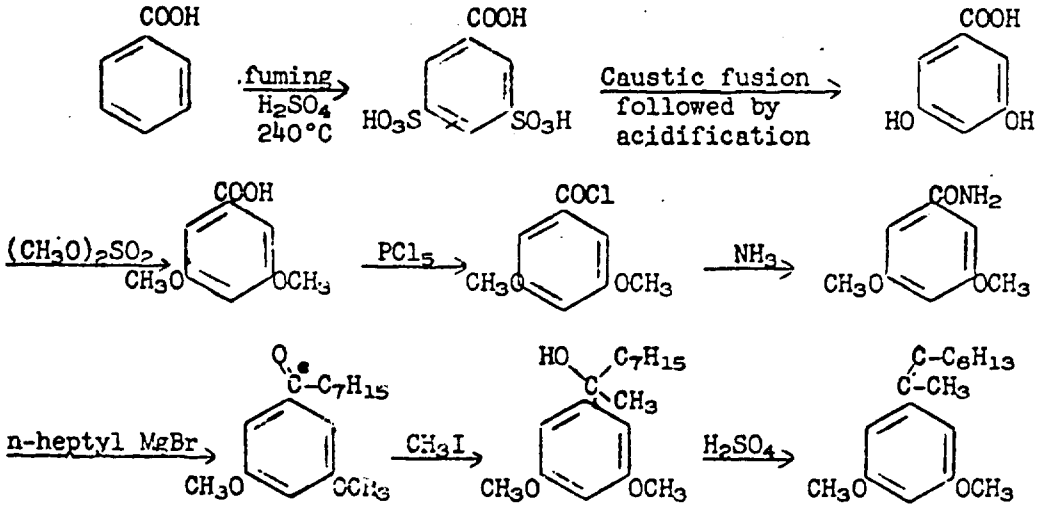
1) Adams, R., MacKenzie, S. and Loewe, S., J Am Chem Soc, 70 664 (1948).

in the left hand ring[1]) such as the elimination of the methyl group or shifting the position of the methyl group failed to offer any improvement. Replacement of both methyls of the pyran group by ethyl or n-propyl groups also was ineffective. Compounds which were 30-500 times more effective than tetrahydrocannabinol were obtained by replacing the n-amyl group on the aromatic ring by longer groups[2)3)4)5)] with methyl groups in the one, or one and two positions.

In this present work it is planned to produce two of Adams' most active compounds, i.e., R = 1-methyloctyl and R = 1,2-dimethylheptyl in structure I. Such changes in structure as the replacement of the pyran oxygen with NH, NR, S, S=O, and SO_2; the replacement of OH on the ring by NH_2, and the introduction of NH_2 in the β-position on the alkyl group are also planned. Some of the nitrogens will be quaternized and carbamate groups will be introduced.

Changes in Alkyl Groups

The first tetrahydrocannabinol analogs to be prepared will be the previously mentioned two most active compounds of Adams. Ethyl 5-methylcyclohexanone-2-carboxylate has been made according to a method given in Organic Syntheses for the prepartion of ethyl cyclohexanone-2-carboxylate from cyclohexanone and diethyl oxalate (see Appendix). The preparation of the desired methyloctyl-resorcinol is being accomplished by the following series of reactions.



1) Adams, R., Smith, C.M. and Loewe, S., J Am Chem Soc, 63,1973 (1941).
2) Adams, R., Chen, K.H. and Loewe, S., J Am Chem Soc 67, 1534 (1945).
3) Adams, R., Aycock, B.F. and Loewe, S., ibid, 70, 662 (1948).
4) Adams, R., MacKenzie, S. and Loewe, S.,ibid, 70, 664 (1948).
5) Adams, R., Harfenish, M. and Loewe, S., ibid, 71, 1624 (1949).

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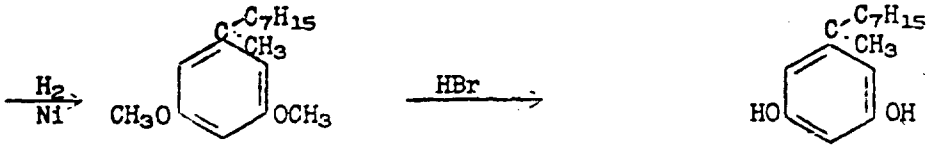


The method used for the preparation of 3,5-dihydroxybenzoic acid was similar to that given in Organic Syntheses but a few modifications have been made in the procedure which decreased the work involved without impairing the yield. This preparation is described in the appendix.

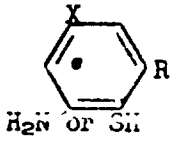
Other methods for preparing 3,5-dihydroxybenzoic acid such as the reduction of 3,5-dinitrobenzoic acid and amide followed by diazotization were tried, but the yields of the dihydroxy compounds were low.

The several steps involved in the conversion of 3,5-dihydroxybenzoic acid to 3,5-dimethoxyphenyl heptyl ketone were carried out according to the procedures described by Suter and Weston.[1] The procedures used for the remainder of the steps are those described by Adams, Chen and Loewe.[2]

At the present time the work on the preparation of 2-(3,5-dimethoxyphenyl)nonane has been carried to 2-(3,5-dimethoxyphenyl)nonene-2. The work on the preparation of 2-(3,5-dimethoxyphenyl)-3-methyl octane is at the stage of 3,5-dimethoxy benzamide.

Nitrogen and Sulfur Analogs

One of the purposes of this problem as stated before is to prepare analogs of tetrahydrocannabinol in which the pyran oxygen is replaced by NH, NR, S, S=O, SO_2, etc. To do this, intermediates of the following composition will have to be prepared.



For this work R will be n-amyl and X may be OH or some group which can be converted to OH after the condensation with ethyl 5-methylcyclohexanone-2-carboxylate. In the case of the thio compound it appears possible that one can use a compound where X is OH for with the mercaptan group being the stronger acid it is felt that the mercaptan group will preferentially enter into the condensation.

1) Suter, C.M. and Weston, A.W., J Am Chem Soc, 61,232 (1939).
2) Adams, R., Chen, K.H., and Loewe, S., J Am Chem Soc, 67, 1536 (1945).

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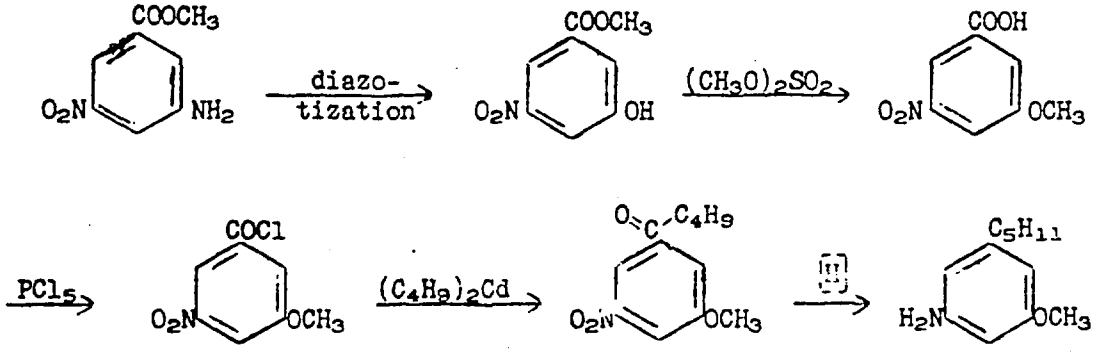
One possible route to 3-mercapto-5-aminobenzoic acid involving the mono-sulfonation of benzoic acid, followed by nitration, conversion to the acid chlorides, and reduction with zinc in acid solution has been carried out but the results are not yet complete. Other proposed routes involve the selective reduction of one nitro group in 3,5-dinitro benzoic acid (or in place of the carboxyl group a group which can be converted to an alkyl group). An attempted partial reduction of 3,5-dinitro benzoic acid with ammonium sulfide according to a method[1] for the reduction of p-nitrophenylacetic acid gave considerable diamino compound. The presence of amino and carboxyl groups in the same molecule made recovery difficult. The partial reduction of 3,5-dinitro-benzamide by a similar method but using less hydrogen sulfide has given some success but the yields are low. Cohen and McCandlish[2] describe the reduction of methyl-3,5-dinitrobenzoate with hydrogen sulfide in methanol using only a trace of ammonium hydroxide. This method has been tried and appears to give yields on the order of 80%. The proposed route from this point will involve the following reactions:



This 1-amyl-3-methoxy-5-aminobenzene may be used directly for the condensation with ethyl 5-methylcyclohexanone-2-carboxylate for the production of a nitrogen analog of tetrahydrocannabinol, or the amino group may be converted to a mercaptan group to give a sulfur analog. It is proposed that once a sulfur analog is prepared it may be oxidized to the S=O, and SO_2 analogs.

1) Robertson, G. R., "Organic Syntheses", Coll. Vol. I, J. Wiley and Sons, Inc., New York, New York, 1941, p 52.
2) Cohen, J. B., and McCandlish, D., J Chem Soc, 87, 1257 (1905).

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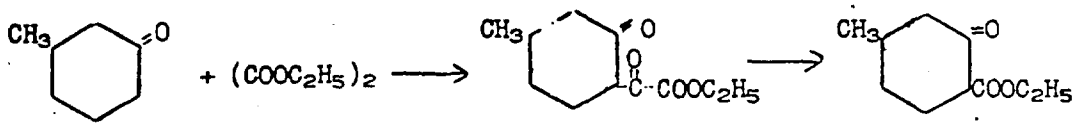
APPENDIX

Ethyl 5-Methylcyclohexanone-2-carboxylate



BP 109-12°C at 10 mm

The Organic Synthesis[1] procedure for ethyl cyclohexanone-2-carboxylate was followed except for substitution of m-methylcyclohexanone for cyclohexanone and the use of dry sodium methoxide rather than sodium ethoxide. The intermediate ethyl 5-methylcyclohexanone-2-glycoxalate boiled at 137-147°C/3 mm during Claisen distillation. The final product obtained in 55% yield was distilled through a packed column at 109-112°C/10 mm.

Anal. Calcd. for $C_9H_{16}O_3$: C, 65.2; H, 8.76; ester 0.543 eq/100 g.
Found: C, 64.8; H, 8.8; ester, 0.542.

1) Snyder, H.R., Brooks, L.A. and Shapiro, S.H., "Organic Syntheses", Coll. Vol. II, John Wiley and Sons, Inc. New York, N.Y.,1943, p 531.

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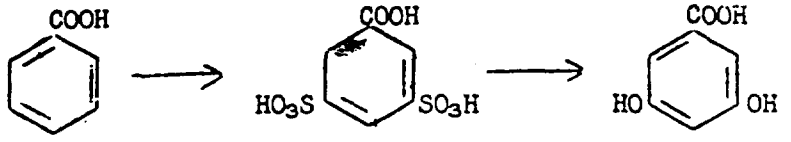
3,5-Dihydroxybenzoic acid



Benzoic acid (2.0 moles, 244 g) and 1100 g of 35% fuming sulfuric acid in a 2-liter flask with condenser were slowly heated to 160-170°C, kept at that temperature overnight and then at 250° for 5 hours. The cold product was poured into 2 liters of water and then into brine (1600 g of salt in 4.5 liters of water). After cooling, the precipitated crude sodium salt of 3,5-disulfobenzoic acid was filtered and dried. The alkali fusion of the crude salt was carried out in a 1200 ml stainless steel beaker following the procedure of Organic Syntheses[1] and the product worked up in much the same way. After crystallization of the crude acid from 500 ml of water, 200 g (65% yield) of dihydroxybenzoic acid, mp 235°, was obtained.

1) Weston, A. W. and Suter, C. M., "Organic Syntheses", Vol. 21, J. Wiley and Sons, Inc., New York, N.Y., 1941, p 27.